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MA(30) Priority: **28.10.2014 IT MI20141845**(71) Applicant: **Cerbios-Pharma S.A.****6917 Barbengo/Lugano (CH)**

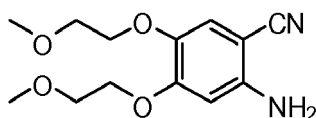
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(74) Representative: **Longoni, Alessandra****AL & Partners Srl****Via C. Colombo ang. Via Appiani****(Corte del Cotone)****20831 Seregno (MB) (IT)**(54) **PROCESS FOR THE PREPARATION OF ERLOTINIB**

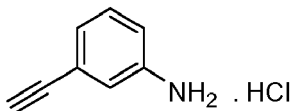
(57) A process for the preparation of Erlotinib comprising:

a) the reaction of the compound of formula (II)



(II)

with the compound of formula (III)



(III)

b) the subsequent treatment with a source of hydrochloric acid in a suitable solvent to give Erlotinib hydrochloride, is described.

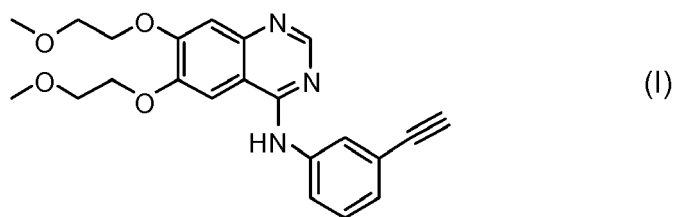
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Description

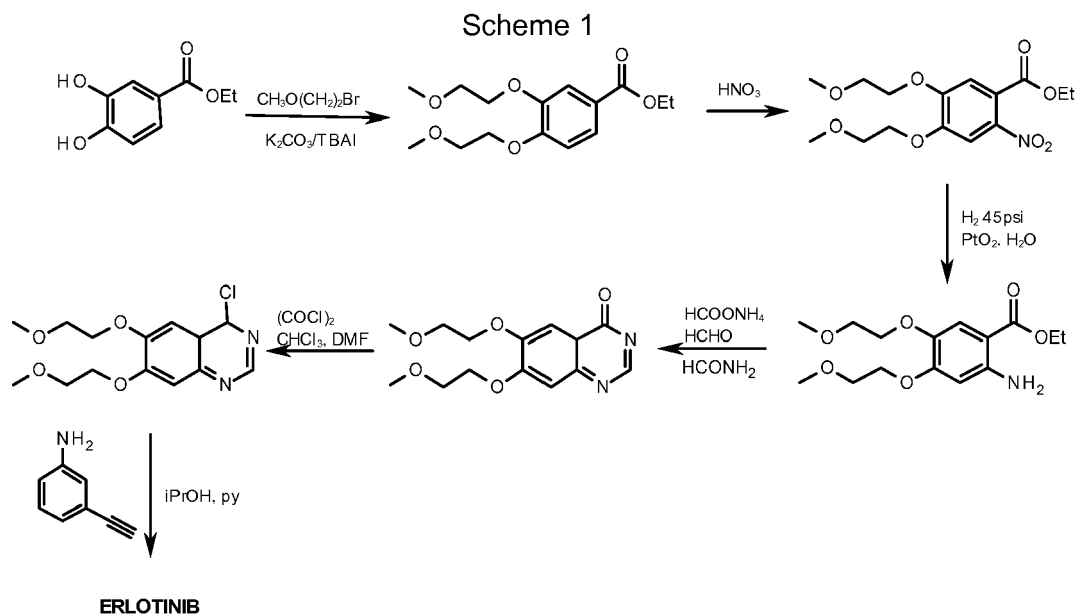
[0001] The present invention relates to a process for the synthesis of Erlotinib and intermediates useful for its preparation.

[0002] Erlotinib is a drug used in the treatment of cancer diseases, in particular for lung and pancreatic cancer. Erlotinib is an inhibitor of the tyrosine kinase receptor, acting in particular by inhibiting the EGF receptor, the epidermal growth factor receptor; in cancer there is the over-expression of growth factor receptors and related ligands. These are, in fact, some of the factors involved in processes of cancer etiopathogenesis. The stimulation of the growth factors leads to an increase of the cell proliferation with the consequent starting of the disease. The receptors, once bound the ligand, self-phosphorylate so generating a cascade of intracellular reactions that lead to the activation of transcription factors involved in the cell proliferation. Erlotinib binds itself to the intracellular catalytic portion of the receptor miming the ATP structure, but being more stable than that, they bind to the receptor and inhibit it. Therefore the activation of the cell reactions is not allowed, so blocking the cell expansion.

[0003] Erlotinib is a compound of formula (I)

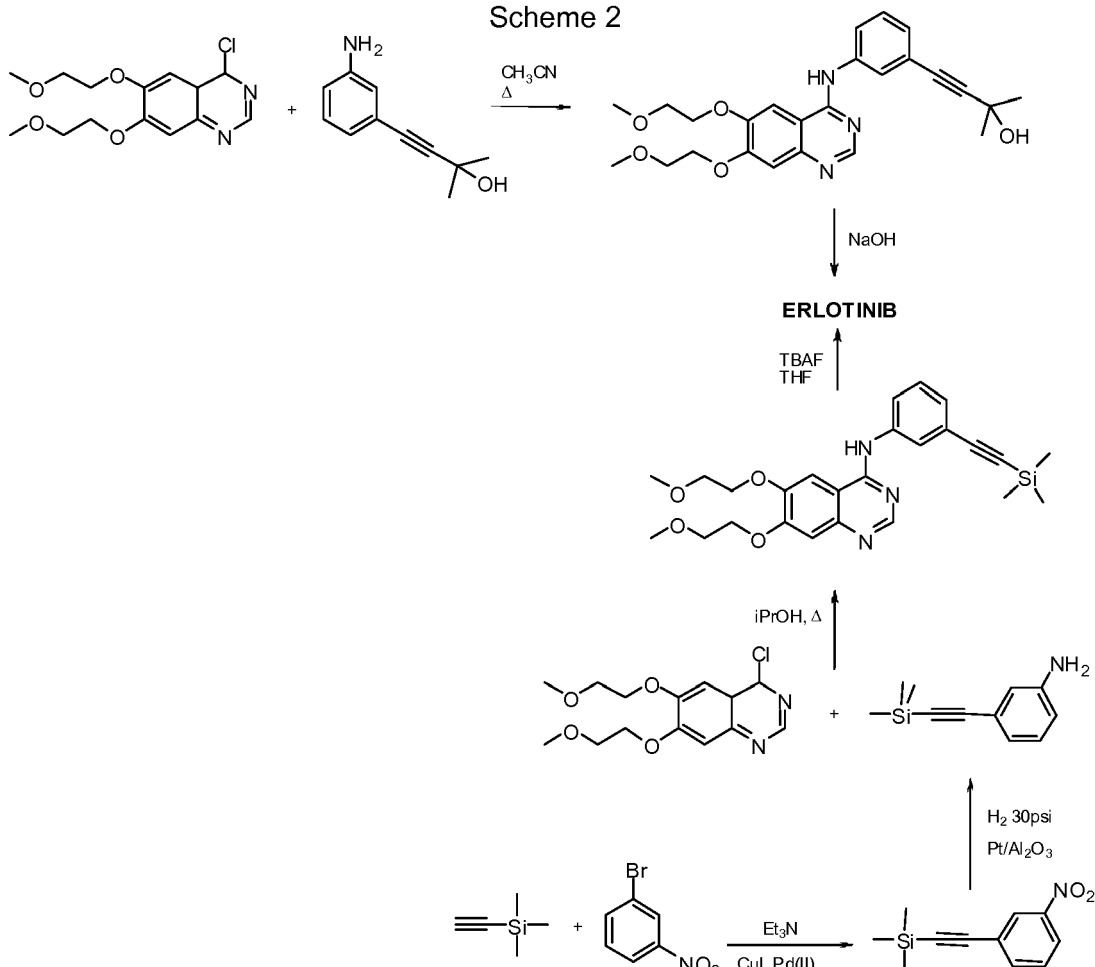


chemically known as *N*-3-(ethynyl-phenyl)-6,7-bis-(2-methoxyethoxy)-4-quinazolin amine, described in WO 96/30347 and marketed with the trademark Tarceva®. WO 96/30347 describes a process for the synthesis of Erlotinib reported in the following scheme 1:



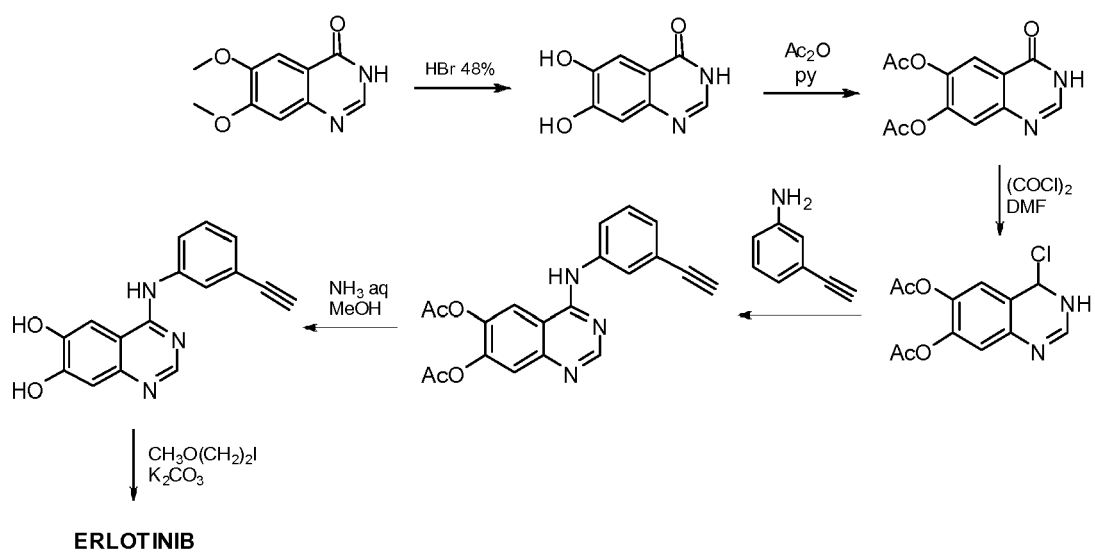
[0004] EP 1 044 969 describes a process for the synthesis of Erlotinib reported in the following scheme 2:

Scheme 2



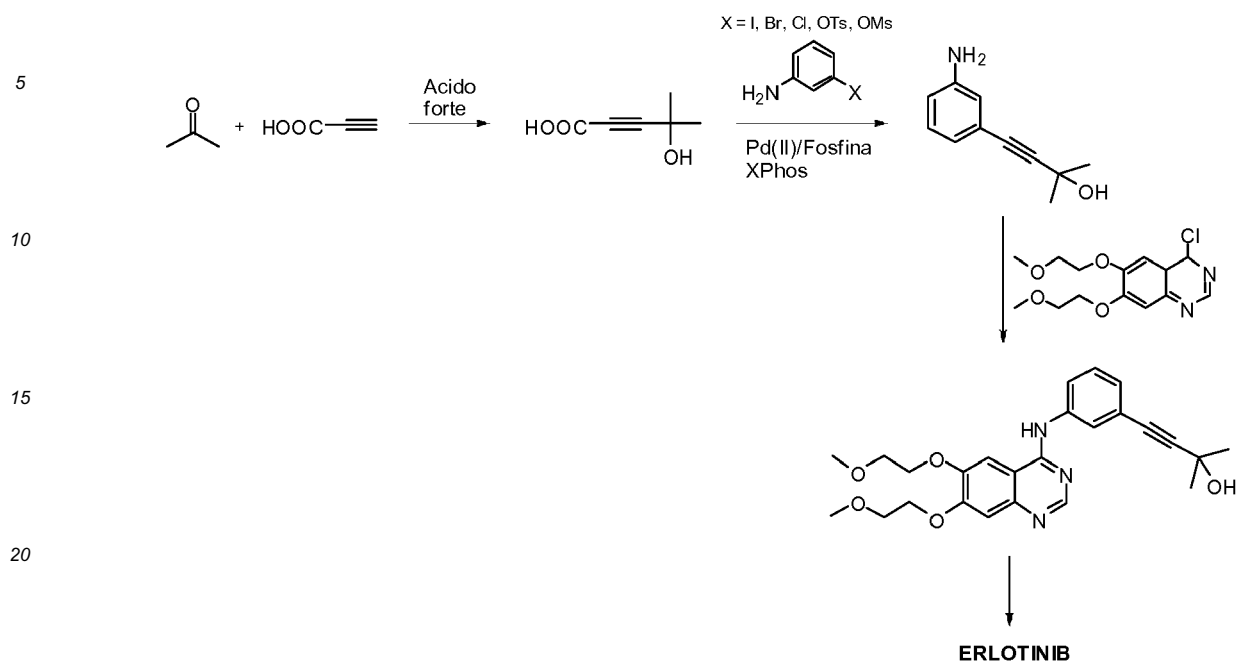
[0005] US 7,960,545 discloses a process for the synthesis of Erlotinib reported in the following scheme 3:

Scheme 3



[0006] EP 2 433 934 describes a process for the synthesis of Erlotinib reported in the following scheme 4:

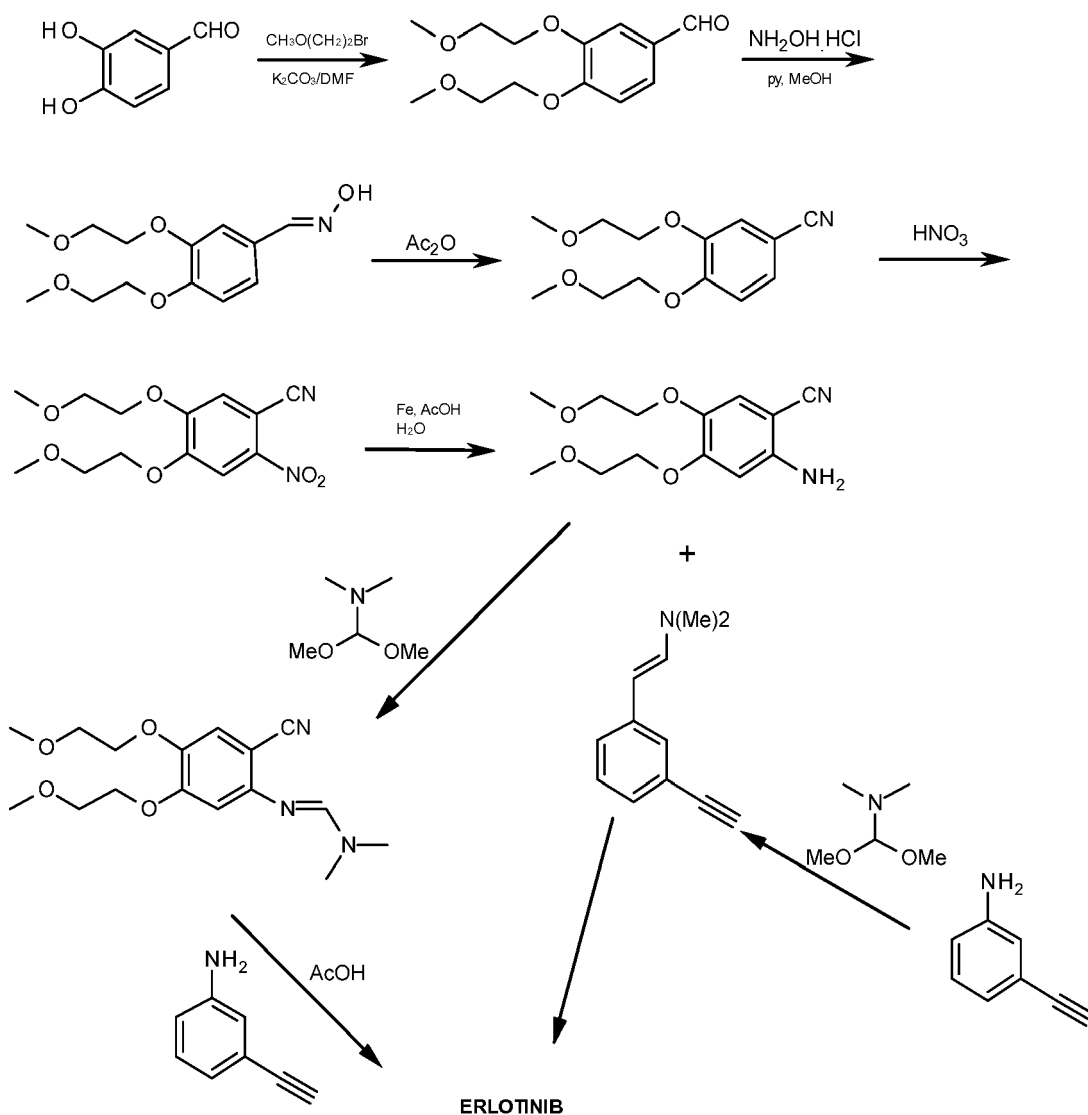
Scheme 4



[0007] All these processes foresee numerous steps for the preparation of the key intermediate, 4-chloro-6,7-bis(2-methoxyethoxy)quinazoline, that is then reacted with 3-ethynylaniline or a derivative thereof.

[0008] WO 2007/138612 and WO 2007/138613 describe a process for the synthesis of Erlotinib reported in the following scheme 5:

Scheme 5

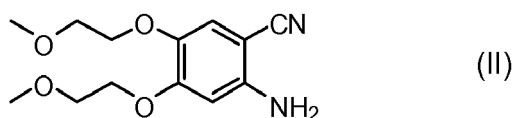


[0009] The processes described in WO 07/138612 and WO 07/138613 have the advantage to reduce the number of steps avoiding the formation and the isolation of the intermediate 4-chloro-6,7-bis(2-methoxyethoxy)quinazoline but they necessarily require the formation and the isolation of the intermediate obtained by the reaction with N,N-dimethylformamide dimethylacetal.

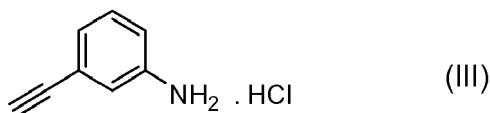
[0010] We have now found that it is possible to further reduce the number of synthetic steps, the use of expensive reagents and the isolation of intermediates so obtaining Erlotinib through a simpler and cheaper process.

[0011] It is therefore object of the present invention a process for the synthesis of Erlotinib comprising:

a) the reaction of the compound of formula (II)



55 with the compound of formula (III)



b) the subsequent treatment with a source of hydrochloric acid in a suitable solvent to give Erlotinib hydrochloride.

[0012] The compounds (II) and (III) are both known and commercially available or prepared according to methods described in literature (for example in WO 2007/138612). The reaction between the compound of formula (II) and the compound of formula (III) of the process object of the present invention is preferably carried out in the presence of trifluoroacetic acid and formamidinium acetate in an aprotic polar solvent selected among acetonitrile, isopropanol, N,N-dimethylformamide, N,N-dimethylacetamide and tetrahydrofuran, preferably acetonitrile.

[0013] The reaction between the compound (II) and the compound (III) represents the most characteristic feature of the process object of the present invention since it allows to carry out one-pot the formation of the quinazoline ring and its functionalization with the 3-ethynylphenylamino group without requiring the isolation of any intermediate and directly obtaining Erlotinib.

[0014] In particular, the use of formamidinium acetate makes the process of the invention different from all the known methods, in particular also from the methods described in WO 07/138612 and in WO 07/138613, which foresee different intermediates and mechanisms of action.

[0015] In the subsequent step of the process object of the present invention a treatment with a source of hydrochloric acid is carried out to obtain Erlotinib hydrochloride. Preferably, the source of hydrochloric acid can be a solution of hydrochloric acid or an amine hydrochloride salt, preferably selected among benzylamine hydrochloride, trimethylamine hydrochloride, triethylamine hydrochloride. An aqueous solution of concentrated hydrochloric acid is more preferably used.

[0016] The treatment with a source of hydrochloric acid is carried out in a suitable solvent preferably selected among isopropanol, methanol, butanol, ethyl acetate and tetrahydrofuran. Isopropanol and ethyl acetate are the most preferred solvents.

[0017] In a preferred embodiment of the process object of the present invention the reaction between the compounds of formula (II) and (III) is carried out in the presence of formamidinium acetate and trifluoroacetic acid in acetonitrile at warm and the subsequent treatment with concentrated hydrochloric acid is carried out in ethyl acetate as solvent, at room or slightly lower temperature. Erlotinib hydrochloride is so obtained with high yield and high degree of purity.

[0018] Although the present invention has been described in its characterizing features, equivalents and modifications obvious to the skilled in the art are included in the present invention.

[0019] The present invention will be now illustrated through some examples without limiting the scope of the invention.

[0020] All the terms used in the present invention, unless otherwise indicated, are to be understood in their common meaning as known in the art. Other more specific definitions for certain terms, as used in the present description, are highlighted herein after and constantly applied in the whole description and claims, unless a different definition provides specifically a broader meaning.

EXAMPLE 1

[0021] In a reaction flask, 2-amino-4,5-bis(2-methoxyethoxy)-benzonitrile (37.01 g, 0.139 mol) and acetonitrile (185 ml) were charged; 3-ethynylaniline hydrochloride (30.00 g, 0.195 mol), trifluoroacetic acid (17.43 g, 0.152 mol) and formamidinium acetate (15.19 g, 0.145 mol) were added to the resultant mixture. The reaction mixture was brought to the reflux temperature of the solvent and maintained under such conditions for about fifteen hours. At the end of the reaction, the temperature was brought to about 25°C, the solvent was removed by distillation under vacuum and methylethylketone (430 ml) was added. The organic phase was washed with a saturated sodium bicarbonate solution (2 x 100 ml) and with water (2 x 100 ml). The collected organic phases were concentrated to residue by distillation under vacuum.

[0022] The resultant raw product was suspended in ethyl acetate (450 ml) and a solution of hydrochloric acid at 37% (14.38 g, 0.145 mol) was added, maintaining the temperature at 15°C for about thirty minutes. The resultant solid was filtered, washed and dried in oven under vacuum at 45°C to give 36.02 g of Erlotinib HCl.

EXAMPLE 2

[0023] In a reaction flask, 2-amino-4,5-bis(2-methoxyethoxy)-benzonitrile (37.01 g, 0.139 mol) and acetonitrile (185 ml) were charged; 3-ethynylaniline hydrochloride (30.00 g, 0.195 mol), trifluoroacetic acid (17.43 g, 0.152 mol) and formamidinium acetate (15.19 g, 0.145 mol) were added to the resultant mixture. The reaction mixture was brought to the reflux temperature of the solvent and maintained under such conditions for about fifteen hours. At the end of the reaction,

the temperature was brought to about 25°C, the solvent was removed by distillation under vacuum and methylethylketone (430 ml) was added. The organic phase was washed with a saturated sodium bicarbonate solution (2 x 100 ml) and with water (2 x 100 ml). The collected organic phases were concentrated to residue by distillation under vacuum.

[0024] The resultant raw product was suspended in ethyl acetate (450 ml) and benzylamine hydrochloride (20.82 g, 0.145 mol) was added, maintaining the temperature at 15°C for about thirty minutes. The resultant solid was filtered, washed and dried in oven under vacuum at 45°C to give 34.31 g of Erlotinib HCl.

EXAMPLE 3

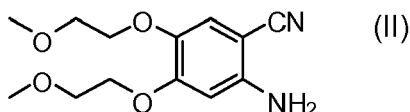
[0025] In a reaction flask, 2-amino-4,5-bis(2-methoxyethoxy)-benzonitrile (37.01 g, 0.139 mol) and acetonitrile (185 ml) were charged; 3-ethynylaniline hydrochloride (30.00 g, 0.195 mol), trifluoroacetic acid (17.43 g, 0.152 mol) and formamidine acetate (15.19 g, 0.145 mol) were added to the resultant mixture. The reaction mixture was brought to the reflux temperature of the solvent and maintained under such conditions for about fifteen hours. At the end of the reaction, the temperature was brought to about 25°C, the solvent was removed by distillation under vacuum and methylethylketone (430 ml) was added. The organic phase was washed with a saturated sodium bicarbonate solution (2 x 100 ml) and with water (2 x 100 ml). The collected organic phases were concentrated to residue by distillation under vacuum.

[0026] The resultant raw product was suspended in ethyl acetate (450 ml) and trimethylamine hydrochloride was added, maintaining the temperature at 15°C for about thirty minutes. The resultant solid was filtered, washed and dried in oven under vacuum at 45°C to give 35.01 g of Erlotinib HCl.

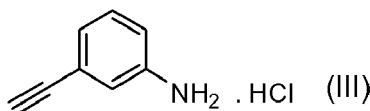
Claims

1. A process for the synthesis of Erlotinib comprising:

a) the reaction of the compound of formula (II)



with the compound of formula (III)



b) the subsequent treatment with a source of hydrochloric acid in a suitable solvent to give Erlotinib hydrochloride.

2. A process according to claim 1 wherein the reaction between the compound of formula (II) and the compound of formula (III) is carried out in the presence of trifluoroacetic acid and formamidine acetate, in an aprotic polar solvent.

3. A process according to claim 2 wherein the aprotic polar solvent is selected among acetonitrile, isopropanol, N,N-dimethylformamide, N,N-dimethylacetamide and tetrahydrofuran.

4. A process according to claim 3 wherein the solvent is acetonitrile.

5. A process according to claim 1 wherein the source of hydrochloric acid is a solution of hydrochloric acid or an amine hydrochloride salt.

6. A process according to claim 5 wherein the amine hydrochloride salt is selected among benzylamine hydrochloride, trimethylamine hydrochloride and triethylamine hydrochloride.

7. A process according to claim 5 wherein the source of hydrochlorid acid is an aqueous solution of concentrated hydrochloric acid.
- 5 8. A process according to claim 1 wherein the treatment with a source of hydrochloric acid is carried out in a solvent selected among isopropanol, methanol, butanol, ethyl acetate and tetrahydrofuran.
9. A process according to claim 8 wherein the solvent is selected between isopropanol and ethyl acetate.
- 10 10. A process according to claim 1 wherein the reaction between the compounds of formula (II) and (III) is carried out in the presence of formamidine acetate and trifluoroacetic acid in acetonitrile at warm and the subsequent treatment with concentrated hydrochloric acid is carried out in ethyl acetate as solvent, at room or slightly lower temperature.

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EUROPEAN SEARCH REPORT

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DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (IPC)
X	CHANDREGOWDA VENKATESHAPPA ET AL: "Convergent Approach for Commercial Synthesis of Gefitinib and Erlotinib", ORGANIC PROCESS RESEARCH AND DEVELOPMENT, AMERICAN CHEMICAL SOCIETY, US, vol. 2007, no. 11, 24 July 2007 (2007-07-24), pages 813-816, XP002498993, ISSN: 1083-6160, DOI: 10.1021/OP700054P [retrieved on 2007-07-24] * Scheme 3; from compound 7 to compound 9 results and discussion * * abstract *	1-10	INV. C07D239/94 A61K31/517 A61P35/00
X	WO 2010/109443 A1 (RANBAXY LAB LTD [IN]; MURUGESAN BALAGURU [IN]; VEMPALI ANANDAM [IN]; S) 30 September 2010 (2010-09-30) * page 4 - page 9; claims 1,6; example 2 *	1-10	
A,D	WO 2007/138612 A2 (VITTAL MALLYA SCIENT RES FOUND [IN]; CHANDREGOWDA VENKATESHAPPA [IN];) 6 December 2007 (2007-12-06) * the whole document *	1-10	TECHNICAL FIELDS SEARCHED (IPC)
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The present search report has been drawn up for all claims			
Place of search Munich		Date of completion of the search 9 November 2015	Examiner Goss, Ilaria
CATEGORY OF CITED DOCUMENTS X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document		T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document	

ANNEX TO THE EUROPEAN SEARCH REPORT
ON EUROPEAN PATENT APPLICATION NO.

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09-11-2015

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- US 7960545 B [0005]
- EP 2433934 A [0006]
- WO 2007138612 A [0008] [0012]
- WO 2007138613 A [0008]
- WO 07138612 A [0009] [0014]
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